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3,7-Dideazaneplanocin: Synthesis and antiviral analysis

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Abstract

Objective: To synthesize 3,7-dideazaneplanocin and evaluate its antiviral potential.

Methods: The target 3,7-dideazaneplanocin has been prepared in five steps from a readily available cyclopentenol. A thorough in vitro antiviral analysis was conducted versus both DNA and RNA viruses.

Results: A rational synthesis of 3,7-dideazaneplanocin was conceived and successfully pursued in such a way that it can be adapted to various analogs of 3,7-dideazaneplanocin. Using standard antiviral assays, no activity for 3,7-dideazaneplanocn was found.

Conclusion: Two structural features are necessary for adenine-based carbocyclic nucleosides (like neplanocin) for potential antiviral properties: (i) inhibition of S-adenosylhomocysteine hydrolase and/or (ii) C-5′ activation via the mono-nucleotide. These two requisite adenine structural features to fit these criteria are not present in in the target 3,7-dideazaneplanocin: (i) an N-7 is necessary for inhibition of the hydrolase and the N-3 is claimed to be essential for phosphorylation at C-5′. Thus, it is not surprising that 3,7-dideazaneplaoncin lacked antiviral properties.

Keywords

Carbocyclic nucleosides, neplanocin, 3,7-dideazaadenine nucleosides, antiviral activity

Introduction

Since the synthesis of aristeromycin **[1]**[1] and its subsequent discovery in nature,[2] carbocyclic nucleosides have received considerable attention as a source of therapeutic agents.[3] Those efforts have led to the clinically useful antivirals entecavir **[2]**[4] and abacavir **[3]** (Figure 1).[5]

Neplanocin A **[4]**, also a naturally occurring adenine-based carbocyclic nucleoside,[6,7] has served a cornerstone framework due to the presence of the cyclopentenyl unit that offers unique conformationally and chemically attractive features for expanding the carbocyclic nucleoside antiviral toolbox. While numerous variations of this center have been productive in the antiviral drug pursuit, modification of the purine ring has been rewarding. In that direction, results from 3-deazaneplanocin **[5]**[8] and 7-deazaneplanocin **[6]**[9] has been encouraging as anti-Ebola,[10] antiorthopox,[11] and anti-HBV and -HCV candidates.[12] Several years ago we sought to combine these two leads with the synthesis and antiviral analysis of 3,7-dideazaneplanocin **[7]**. The results from this investigation are presented here.

Results and discussion

Synthesis

The synthesis of target **[7]** began by, first, converting the requisite trityl protected cyclopentenol **[8]**[13] into mesylate **[9]**. This product was, in turn, reacted with 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine[14,a,b] in the presence of sodium hydride to provide **[10]**, which was converted directly to the hydrazine derivative **[11]**. Raney nickel promoted reduction of **[11]** to **[12]** followed by acid catalyzed deketalization resulted in the desired **[7]** (Scheme 1).

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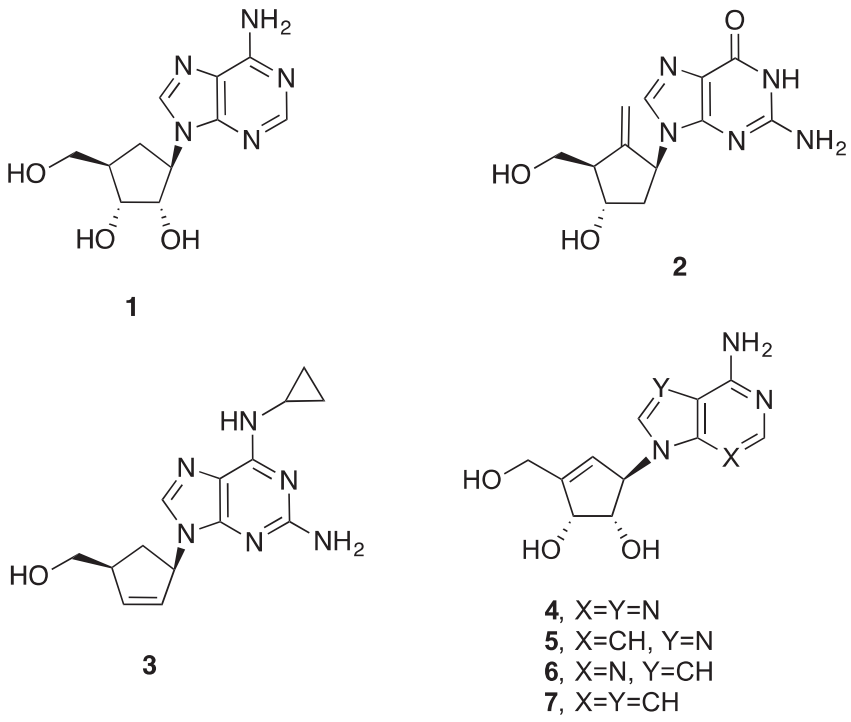
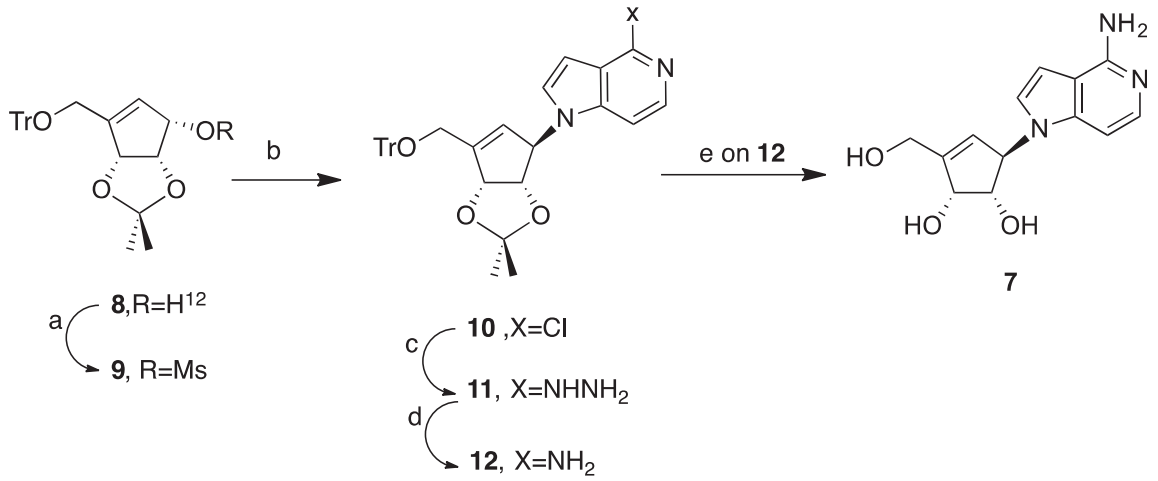


Figure 1. Aristeromycin, neplanocin A and related synthetic analogs.



Scheme 1. Synthesis of **[7]**. a, MsCl, Et_3N, CH_2Cl_2; b, 4-chloro-1H-pyrrolo[3,2-c]-pyridine, NaH, DMF; c, hydrazine monohydrate, 2-methoxyethanol; d, Raney Ni, H_2O, 30% (from 8); e, 0.5 N HCl, MeOH, 92%.

Antiviral results

Compound **[7]** was evaluated[15] versus a number of viruses and found to be inactive.[c]

Conclusion

Two structural features are necessary for adenine-based carbocyclic nucleosides to demonstrate potential antiviral properties: (i) inhibition of S-adenosylhomocysteine hydrolase[16] and/or (ii) C-5′ activation via the mono-nucleotide.[16] These two requisite adenine structural features that fit these criteria are not present in **[7]**: (i) an N-7 is necessary for inhibition of the hydrolase[9] and (ii) the N-3 is claimed to be essential for phosphorylation at C-5′.[16] These observations may account for the lack of antiviral activity for **[7]**.

Experimental section

Chemistry

The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AV 600 spectrometer (600 MHz for proton and 150 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane at 0.0 ppm. The reactions were monitored by thin-layer chromatography using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, and 60 Å using elution with the indicated solvent system.

1-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-6-((trityloxy)methyl)-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-1*H*-pyrrolo[3,2-c]pyridin-4-amine [12]). To a solution of **[8]**[13] (400 mg, 2.56 mmol) and triethylamine (0.46 ml) in anhydrous CH_2Cl_2 (20 ml) was added MsCl (0.2 ml, 2.56 mmol) at 0 °C. The reaction mixture gave a yellow solution after stirring 1 h at room temperature. It was then diluted with CH_2Cl_2 (20 ml) and washed with icy water (20 ml), dried (Na_2SO_4), and filtered. Evaporation of filtrate provided **[9]** as a sticky yellow oil, which was directly used for the next step.

To a solution of **4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine**[14a,b] (479 mg, 3.13 mmol) in dry DMF (20 ml) was added NaH (74.0 mg, 3.13 mmol). This mixture became a clear dark solution after 0.5 h at room temperature and the above oil **[9]** in DMF (20 ml) was added. The reaction mixture was then kept at 80 °C for 36 h and the DMF removed and evaporated to give a black residue. Water (20 ml) was added and the aqueous phase extracted with EtOAc (2 × 20 ml). The combined organic layers were dried (anhyd. Na_2SO_4), filtered, and evaporated under reduced pressure. The residue **[10]** as a white foam was used directly in the next step.

To a solution of **[10]** from the last process in 2-methoxyethanol (10 ml) was added hydrazine monohydrate (10 ml). The reaction mixture was then refluxed overnight. The solvents were evaporated in vacuo to give a sticky oil **[11]**. This oil was then suspended in H_2O and N_2 was bubbled into this mixture for 20 min. Raney nickel (2.0 g in H_2O) was added and the mixture was stirred at reflux for 3 h. The hot solution was filtered through a pad of Celite that was repeatedly washed with MeOH. The MeOH was then evaporated under reduced pressure to give a pink residue. Column chromatography of this material using hexanes–EtOAc (4:1) gave **[12]** (550 mg, 30% in four steps from **[8]**) as white foam, mp 179–181 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 6.4 Hz, 1 H), 7.50–7.46 (m, 6 H), 7.35–7.22 (m, 9 H), 6.92 (m, 2 H), 6.54 (d, *J* = 3.2 Hz, 1 H), 6.11 (s, 1 H), 5.50 (brs, 2 H), 5.42 (s, 1 H), 5.16 (d, *J* = 5.78 Hz, 1 H), 4.50 (d, *J* = 5.78 Hz, 1 H), 3.99 (d, *J* = 15.2 Hz, 1 H), 3.87 (d, *J* = 15.2 Hz, 1 H), 1.44 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 152.2, 149.4, 143.9, 140.4, 136.5, 128.7, 128.2, 127.4, 124.3, 122.9, 112.7, 111.7, 100.5, 98.8, 87.5, 85.2, 84.1, 77.4, 67.1, 27.6, 26.1. Anal. Calcd for $C_{35}H_{33}N_3O_3 \cdot H_2O$: C, 74.77; H, 6.23; N, 7.48; Found: C, 74.85; H, 6.40; N, 7.24.

(1*S*,2*R*,5*R*)-5–(4-amino-1*H*-pyrrolo[3,2-*c*]pyridin-1-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol [7]). Compound **[12]** (520 mg, 1.92 mmol) was dissolved in 1 N HCl (20 ml) in MeOH. This mixture was stirred at room temperature for 0.5 h and then evaporated to dryness under reduced pressure. The residue was then dissolved in MeOH and neutralized with IRA-67 resin and then purified by column chromatography (MeOH–EtOAc, 1:5) to give **[7]** (92%) as a white solid, mp >187 °C (dec); ^{1}H NMR (DMSO, 400 MHz) δ 8.25 (brs, 2 H), 7.59 (d, *J* = 7.0 Hz, 1 H), 7.31(d, *J* = 3.2 Hz, 1 H), 7.17 (d, *J* = 7.0 Hz, 1 H), 7.06 (d, *J* = 3.21 Hz, 1 H), 5.71 (s, 1 H), 5.41 (s, 1 H), 5.28 (d, *J* = 7.40 Hz, 1 H), 5.14 (m, 1 H), 5.02 (m, 1 H), 4.35 (s, 1 H), 4.13 (m, 2 H), 3.88 (q, *J* = 5.8 Hz, 1 H); ^{13}C NMR (DMSO, 400 MHz) δ 151.0, 150.0, 139.5, 127.9, 125.9, 123.0, 109.6, 103.2, 99.1, 78.7, 72.0, 66.5, 58.6; Anal. Calcd $C_{13}H_{15}N_3O_3 \cdot 0.8\ H_2O$: C, 56.58; H, 6.02; N, 15.23; Found: C, 56.78; H, 5.81; N, 14.91.

Antiviral assays

These assays are presented in Chen et al.[15]

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Declaration of conflicting interests

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Notes

a. Using modification of a reported procedure.

b. Recently commercially available (Sigma-Aldrich, 28 June 2017).
c. There was no activity for **[7]** (host cell) for toward (EC50 values in μM): cowpox (HFF, >300), vaccinia (HFF and E6SM, >300), rhinovirus (Hela Ohio-1, >100), adenovirus (A-549, >100), respiratory syncytial virus (HeLa and MA-104, >200), influenza A (H3N2) (MDCK, >100), PIV (MA-104, >100), SARS corona (Vero 76, >100), dengue (Vero, >52), West Nile (Vero, >100), hepatitis C (Huh-5-2, >52), HSV 1 and 2 (E6SM, >60), Tacaribe (BS-C-1, >100), HCMV AD 169 and Davis (HEL, >100), VZV TK+ and TK- (HEL >60), HIV-1 and HIV-2 (CEM, >50), parainfluenza virus 3 (Vero, >200), reovirus-1 (Vero, >200), Sindbis virus (Vero, >200), Coxsackie virus B4 (Vero, >200), Punto Toro virus (Vero, >200), vesicular stomatitis virus (E6SM, >200), HBV (HepG2 2.2.15, >10), yellow fever (Vero, >100), and measles (CV-1, >100).

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